Remarks

The Amendments

The specification has been amended so that the SEQ ID NOs in the specification match with the amended sequence listing containing 33 sequences. The claims have also been amended to be consistent with the sequence listing. Substitute sheets comprising the amended claims and specification are attached. No new matter is added by these amendments. Applicant respectfully requests entry of these amendments.

Non-Establishment of Opinion with Regard to Novelty, Inventive Step, and Industrial Applicability

The Written Opinion asserts that an opinion with regard to novelty, inventive step, and industrial applicability cannot be formulated for claims relating to a polypeptide comprising the amino acid sequence of SEQ ID NO:27 (now SEQ ID NO:24), or a polypeptide encoded by a polynucleotide of SEQ ID NO:1. The Written Opinion asserts that SEQ ID NO:1 does not comprise an ORF that leads to a translated product and that SEQ ID NO:27 (now SEQ ID NO:24) is not the translational product of SEQ ID NO:1. The Written Opinion concludes that the polypeptide of SEQ ID NO:27 (now SEQ ID NO:24) does not exist and that SEQ ID NO:1 does not encode a polypeptide, and therefore an opinion with regard to novelty, inventive step, and industrial applicability for claims referring to polypeptides cannot be formulated (claims 1-3, 5, 13, 14, 18-28, and 30-32, completely, 9-12 and 15-17 partially).

SEQ ID NO:1 (DST IMX4) was used to isolate a sequence (SEQ ID NO:11) that included DST IMX4 (SEQ ID NO:1). See specification page 59, Example 2; Exhibit A, a BLAST result showing that SEQ ID NO:11 includes SEQ ID NO:1. An approximately 2.0 kb clone was isolated from a commercial library. The sequence of the 3' end of the clone (SEQ ID NO:12) included the sequence of IMX 4 DST (SEQ ID NO:1). See specification

page 59, Example 2, and Exhibit B, a BLAST result showing that SEQ ID NO:12 includes SEQ ID NO:1.

A partial translation of SEQ ID NO:11 comprises the amino acid of SEQ ID NO:27 (now SEQ ID NO:24). See Exhibit C, a BLAST result showing that a translation of SEQ ID NO:11 comprises SEQ ID NO:27 (now SEQ ID NO:24). Therefore, the larger clone (SEQ ID NO:11) that was isolated using SEQ ID NO:1 and that comprises a part of SEQ ID NO:1, does translate to SEQ ID NO:27 (now SEQ ID NO:24). Therefore, SEQ ID NO:27 (now SEQ ID NO:24) is related to SEQ ID NO:1, and does exist. Applicants respectfully request that SEQ ID NO:27 (now SEQ ID NO:24) be examined on its merits.

Reasoned Statement Under Rule 66.2(a)(ii)

The Written Opinion asserts that claims 9-12 and 15-17 are not novel in view of D1 or D2. The claims have been amended so that language referring to polynucleotides that are "at least 95% identical to SEQ ID NO:1" has been eliminated. D1 and D2 do not teach or suggest the polynucleotide shown in SEQ ID NO:1. SEQ ID NO:1 novel in view of D1 and D2. The rejection is therefore moot in view of the amendments.

The Written Opinion asserts that claims 4, 6-12, 15-17, and 29 lack inventive step because the specific function of the polynucleotide shown in SEQ ID NO:1 is unknown and therefore cannot solve any problem.

The specification teaches that damage to the intestinal epithelial barrier is a hallmark of inflammatory bowel diseases (IBD) and that the T84 intestinal epithelial barrier system is an *in vitro* model of epithelial barrier function. See page 1, lines 14-15; page 57, lines 25-29. The specification teaches that the model responds to proinflammatory cytokines, such as interferon-gamma, by decreasing barrier function and by up-regulating MHC Class II molecules and antigen presenting activity. This model was used to examine how the epithelial barrier is regulated by various genes such as interferon-gamma. According to the

specification, the T84 model assists in the elucidation of the mechanism of barrier breakdown and recovery in response to these agents and in the identification or proteins and genes that may prevent barrier breakdown or stimulate barrier recovery. See page 2, lines 1-10. Therefore, proteins and genes up- or down-regulated in the T84 system in response to barrier breakdown are useful in, for example, the prevention of barrier breakdown in IBD, the stimulation of barrier recovery in IBD, and the diagnosis of IBD. See pages 43, line 1 through page 54, line 27.

The knowledge of the specific function of a particular polypeptide or polynucleotide of the invention is not necessarily important for uses such as methods of diagnosis (see e.g. amended claims 27-32) or methods for preventing, treating, modulating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of a polypeptide or polynucleotide of the invention (see e.g. claims 23-26). Therefore, the knowledge of the specific function of a polypeptide or polynucleotide of the invention is not critical to the invention. Instead, the knowledge of the fact that the polypeptide or polynucleotide of the invention is up- or down-regulated when there is damage to an epithelial barrier demonstrates that the polypeptide or polynucleotide is useful in, for example, the prevention of barrier breakdown in IBD, the stimulation of barrier recovery in IBD, and diagnosis of IBD.

Therefore, the amended claims of the application do comprise an inventive step.

Defects in the International Application

First, the Written Opinion states that point (d) of claim 9 is lacking. This claim has been rewritten and is no longer lacking a point (d).

Second, the Written Opinion asserts that sequences of SEQ ID NO:11 and SEQ ID NO:12 do not include the sequence of SEQ ID NO:1. As discussed above and demonstrated in Exhibits A and B, SEQ ID NO:11 and SEQ ID NO:12 do include SEQ ID NO:1.

Third, the Written Opinion asserts that the specification does not define SEQ ID NOs:18, 19, and 21-26 although they are mentioned in the claims. The specification, claims, and sequence listing have been amended so that the SEQ ID NOs in the specification and claims match those in the sequence listing.

Fourth, the Written Opinion asserts that claims 16 and 29 do not describe how the claimed methods are to be performed. Claim 16 has been replaced by claim number 15 and the claim now states that the method of making the recombinant host cell comprises transforming a host cell with a nucleic acid molecule of claim 1. Claim 29 has been replaced with claims 27 and 28, which are reproduced below:

> 27. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:
> (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
> (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.
> 28. The method of claim 27 wherein the pathological condition is inflammatory bowel disease.

Claims 27 and 28 provide the methods by which the method of diagnosis it to be performed. The claims specify that the method comprises determining the presence or absence of a mutation in a polynucleotide of the invention and diagnosing a pathological condition based on the presence or absence of the mutation. The methods are clearly stated in these claims.

Certain Observations on the International Application

First, the Written Opinion states that the formulation "comprises" in claims 4 and 8-12 do not clearly define the scope of the claims and should be replaced with "consists of." The claims have been amended. In view of the amendments, Applicant believes the rejection is moot.

Second, the Written Opinion states that claims 9 and 12 lack clarity due to the use of "hybridizable to." The claims have been rewritten. Claim 6 now recites "An isolated nucleic acid molecule at least ten bases in length that is hybridizable to the isolated nucleic acid molecule of claim 1 under stringent conditions." The specification clearly states that "Stringent hybridization conditions" refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C. See page 11, lines 26-32. One of skill in the art would understand the meaning of "hybridizable to the isolated molecule of claim 1 under stringent conditions," given the description in the specification of "stringent hybridization conditions."

Third, the Written Opinion asserts that claim 1 does not provide evidence of altered expression of SEQ ID NO:1 in a T84 model of gut barrier function. The specification does provide such evidence (see e.g., Table 1); however, the claims have been amended to remove this language.

Fourth, the Written Opinion asserts that claim 29 is not based on the description. Claim 29 has been amended to read:

> A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising detecting an alteration in expression of a polypeptide of claim 3, wherein the presence of an alteration in expression of the polypeptide is indicative of the pathological condition or susceptibility to the pathological condition.

The specification teaches that a polypeptide having an amino acid sequence shown in SEQ ID NO:27 (now SEQ ID NO:24) is altered in the T84 system in response to barrier breakdown. See Table 1. The specification further teaches that the detection of such an alteration in

expression is indicative of a pathological condition or susceptibility to a pathological condition. Therefore, amended claim 29 is supported by the specification and one of skill in the art could perform the claimed method. See e.g., page 58, lines 26-31.

Respectfully submitted,

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